TOBACCO INDUSTRY RESEARCH COMMITTEE #187
150 EAST FORTY SECOND STREET NEW YORK 17, N.Y.

Application For Research Grant

Date: December 13, 1957

1. Name of Investigator: Herbert Silvette, B. S., M. S., Ph. D.

2. Title: Visiting Professor Pharmacology

3. Institution & Address: Medical College of Virginia
Richmond 19, Virginia

4. Project or Subject: Immunological Investigation of Tobacco and Tobacco Smoke

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

A survey of the literature (H. Silvette, P. S. Larson & H. B. Haag, "Immunological Aspects of Tobacco and Smoking," American Journal of Medical Sciences 234:561-589, 1957, discloses that virtually no fundamental experimental work on animals has been performed in connection with the immunology of tobacco. That tobacco, or its extracts or smoke, may elicit positive skin reactions in man which are true antigen - antibody reactions has been unequivocally demonstrated, which encourages belief in the probability that, under optimal conditions and in susceptible species, antibody responses to tobacco antigens may also be elicited and studied in animals.

The program for such an investigation will be essentially a classic study of the immunology of any presumed antigenic substance. The first step will be to actively sensitize rabbits and guinea pigs to (1) tobacco, both green and cured, of various strains; (2) tobacco extracts prepared in various ways; (3) tobacco smoke; and (4) extracts of tobacco smoke. Standard intravenous injection schedules will be used, and also subcutaneous and intraperitoneal injection of the several materials prepared with Freund's adjuvant. In the case of tobacco smoke, the attempt will be made to actively sensitize guinea pigs through tobacco-smoke exposure, and also to shock passively sensitized guinea pigs by inhalation of tobacco smoke. From time to time, rabbit immune serum

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will be tested for precipitins against one or more antigens, and the animals themselves tested for Arthus and skin reactions. Guinea pigs will be given challenging injections of various antigens. Once a workable technique has been evolved for good immunization, and a potent rabbit immune serum available, cross-immunization and cross-precipitin tests will be carried out using suitable extracts of varieties of tobaccos, smoking forms, and commercial brands of cigarettes. In addition, the immunology of tobacco pollen and tobacco seeds will be investigated.

While there is no experimental evidence that nicotine per se is antigenic, there are a number of observations which indicate that nicotine may influence immune reactions. An attempt will be made to determine whether nicotine may act as a haptene. That this may occur in disease in man, through combination with some body protein, has been suggested as a possibility. Experimentally, active immunization of animals with nicotine deliberately so combined, would be of very considerable theoretical and clinical importance, if successful. A number of techniques to test this possibility have been tentatively formulated. Animals immunized with such nicotine-protein complexes will be challenged with the original nicotine-protein mixture, the protein alone, and nicotine alone.

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6. Budget Plan: (First year)

Salaries Social Security	12,100
Expendable Supplies	1,650
Permanent Equipment	500
Overhead	1,475
Other (Travel)	300
Total	16,225

7. Anticipated Duration of Work: Two years

8. Facilities and Staff Available: Animal quarter and caging facilities, centrifuge, constant temperature baths, incubators, etc., needed for the type of work proposed. The support of the pharmacology staff as needed.

9. Additional Requirements: In the salary item listed in (6) are budgeted $7500 for the principal investigator, $4000 for a trained technician and $600 for a part time animal man.

10. Additional Information (Including relation of work to other projects and other sources of supply):

The principal investigator has been interested in immunopharmacology for many years, and in 1952-53 was head of the Allergy Research Laboratory, University of Virginia Medical School. Further research in immunopharmacology was carried out during 1953-54 in the Department of Pharmacology, University of Washington Medical School. Publications in the field of immunology include:"Antigen system of acacia," Fed. Proc. 12:1210, 1953 (H. Silvette and O. Swineford, Jr.). "A protein precipitating polysaccharide from acacia," Fed. Proc. 13:1329, 1954 (H. Silvette). "Observations on acacia as an immunizing, sensitizing, anaphylactogenic, and desensitizing antigen," J. Allergy 26:509, 1955 (H. Silvette, O. Swineford,Jr. and L. Tull).

Concerning supplies of tobacco materials for this project, it is hoped that many if not all of the various tobacco fractions that will be studied can be obtained from the Tobacco Industry.

Signature Herbert Silvette
Director of Project

W. F. Tompkins
Business Officer of the Institution
Comptroller

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